C.2 Research in Progress

The theory discovery project has two major goals over the next several months: first, to complete construction of a knowledge base that can be used to model and simulate the structure-function relationships relevant to genetic regulation, and second, to complete initial design of a computational architecture for theory extension, improvement, and discovery.

C.2.1 Building a Simulatable Model

The initial knowledge base will contain information relevant to genetic regulation in general and to the trp operon system in particular. The information will relate both to structure, i.e. the physical characteristics of the biological objects, and to function, i.e. the operational characteristics of the biological objects. In addition, the procedural knowledge needed to relate structure to function will play an important part in the knowledge base.

The goal is to have a knowledge base that can be used "actively" to simulate the result of various possible changes in the underlying regulatory model. For example, a common experimental method for studying a biological system is to introduce a mutation which destroys the functionality of some piece of the system. The regulatory knowledge base should be able to simulate and describe the results of such a "deletion mutation."

C.2.2 Design of Discovery System Architecture

In parallel with our work on knowledge base construction, we are designing an initial architecture for theory proposal, extension, and correction. In human scientists we have observed at least four major types of reasoning during the cognitive process. The first is data-driven reasoning when the major goal is to explain individual experimental results. The second is theory-driven reasoning which occurs when a partial theory or model drives its own extension. The third type of reasoning involves looking at closely related biological systems (e.g, noticing a similar behavior in the his operon system). The final type of reasoning relates to more distant analogies; thinking of DNA polymerase moving along a nucleotide sequence as similar to a railroad engine moving along a set of tracks. Our discovery system architecture will be able to embrace all of these reasoning types. A blackboard-style hybrid architecture is our initial guess, but much theoretical and experimental work needs to be done before we are satisfied with our architectural decisions.

D. Publications

1. Bach, R., Friedland, P., Brutlag, D. and Kedes, L.: *MAXIMIZE, a DNA sequencing strategy advisor*. Nucleic Acids Res. 10(1):295-304, January, 1982.

2. Bach, R., Friedland, P., and Iwasaki, Y.: *Intelligent computational assistance for experiment design*. Nucleic Acids Res. 12(1):11-29, January, 1984.

3. Brutlag, D., Clayton, J., Friedland, P. and Kedes, L.: *SEQ: A nucleotide sequence analysis and recombination system*. Nucleic Acids Res. 10(1):279-294, January, 1982.

4. Clayton, J. and Kedes, L.: *GEL, a DNA sequencing project management system*. Nucleic Acids Res. 10(1):305-321, January, 1982.

5. Feitelson, J. and Stefik, M.J.: *A case study of the reasoning in a genetics experiment*. Heuristic Programming Project Report HPP-77-18 (working paper), May, 1977.

6. Friedland, P.: *Knowledge-based experiment design in molecular genetics.* Proc. Sixth IJCAI, August, 1979, pp. 285-287.

7. Friedland P.: *Knowledge-based experiment design in molecular genetics.* Stanford Computer Science Report STAN-CS-79-760 (Ph.D. thesis), December, 1979.

8. Friedland, P., Kedes, L. and Brutlag D.: *MOLGEN--Applications of symbolic computation and artificial intelligence to molecular biology.* Proc. Battelle Conference on Genetic Engineering, April, 1981.

9. Friedland, P.: *Acquisition of procedural knowledge from domain experts.* Proc. Seventh IJCAI, August, 1981, pp. 856-861.

10. Friedland, P., Kedes, L., Brutlag, D., Iwasaki, Y. and Bach R.: *GENESIS, a knowledge-based genetic engineering simulation system for representation of genetic data and experiment planning.* Nucleic Acids Res. 10(1):323-340, January, 1982.

11. Friedland, P. and Iwasaki Y.: *The concept and implementation of skeletal plans.* (To appear in J. Artificial Intelligence, 19834

12. Friedland, P., Armstrong, P., and Kehler, T.: *The role of computers in biotechnology.* BIO\TECHNOLOGY 565-575, September, 1983.

13. Iwasaki, Y. and Friedland, P.: *SPEX: A second-generation experiment design system.* Proc. of Second National Conference on Artificial Intelligence, August, 1982, pp. 341-344.

14. Martin, N., Friedland, P., King, J. and Stefik M.J.: *Knowledge base management for experiment planning in molecular genetics.* Proc. Fifth IJCAI, August, 1977, pp. 882-887.

15. Meyers, S. and Friedland, P.: *Knowledge-based simulation of regulatory genetics in bacteriophage Lambda.* Nucleic Acids Res. 12(1):1-9, January, 1984.

16. Stefik, M. and Friedland, P.: *Machine inference for molecular genetics: Methods and applications.* Proc. of NCC, June, 1978.

17. Stefik, M.J. and Martin N.: *A review of knowledge based problem solving as a basis for a genetics experiment designing system.* Stanford Computer Science Report STAN-CS-77-596, March, 1977.

18. Stefik, M.: *Inferring DNA structures from segmentation data: A case study.* Artificial Intelligence 11:85-114, December, 1977.

19. Stefik, M.: *An examination of a frame-structured representation system.* Proc. Sixth IJCAI, August, 1979, pp. 844-852.

20. Stefik, M.: *Planning with constraints.* Stanford Computer Science Report STAN-CS-80-784 (Ph.D. thesis), March, 1980.

E. Funding Support

The MOLGEN grant is titled: MOLGEN: Applications of Artificial Intelligence to Molecular Biology: Research in Theory Formation, Testing, and Modification. It is NSF Grant MCS-8310236. Current Principal Investigators are Edward A. Feigenbaum Professor of Computer Science and Charles Yanofsky, Professor of Biology. MOLGEN is currently funded from 11/83 to 10/84 at $139,215 including indirect costs as the first year of a three year grant.

II. INTERACTIONS WITH THE SUMEX-AIM RESOURCE

SUMEX-AIM continues to provide the bulk of our computing resources. The facility has not only provided excellent support for our programming efforts but has served as a major communication link among members of the project. Systems available on SUMEX-AIM such as INTERLISP, TV-EDIT, and BULLETIN BOARD have made possible the project's programming, documentation and communication efforts. The interactive environment of the facility is especially important in this type of project development.

We strongly approve of the network-oriented approach to a programming environment that SUMEX has begun to evolve into. The ability to utilize LISP workstations for intensive computing while still communicate with all of the other SUMEX resources has been very valuable to our work. We see a satisfactory mode of operation where most programming takes place on the workstations and most electronic communications, information sharing, and document preparation takes place within the mature TOPS-20 environment. The evolution of SUMEX has alleviated most of our previous problems with resource loading and file space. Our current workstations are not quite fast nor sophisticated enough, but we are encouraged by the progress that has been made.

We have taken advantage of the collective expertise on medically-oriented knowledge-based systems of the other SUMEX-AIM projects. In addition to especially close ties with other projects at Stanford, we have greatly benefited by interaction with other projects at yearly meetings and through exchange of working papers and ideas over the system.

The ability for instant communication with a large number of experts in this field has been a determining factor in the success of the MOLGEN project. It has made possible the near instantaneous dissemination of MOLGEN systems to a host of experimental users in laboratories across the country. The wide-ranging input from these users has greatly improved the general utility of our project.

We find it very difficult to find fault with any aspect of the SUMEX resource management. It has made it easy for us to expand our user group, to give demonstrations (through the 20/20 adjunct system as well as the LISP workstations), and to disseminate software to non-SUMEX users overseas.

III. RESEARCH PLANS

A. Project Goals And Plans

Our current work has the following major goals

1. Build a knowledge base that can be used for regulatory system simulation purposes. The knowledge base will represent the current model of an explanatory theory. We have already scoped the contents of this knowledge base and have begun construction.

2. Use the simulation knowledge base to explain observations that are indeed explainable without changes to the current model.

3. Begin to recognize when observations are "interesting" in that they contradict, dramatically confirm, are or unpredictable by the current model.

4. Build a mechanism for postulating extensions or corrections to the current theory: a constrained regulatory theory generator. Here are where the major AI architectural decisions will be made.

5. Build a mechanism for evaluating alternative theories.

6. Test this entire structure on the evolving trp regulatory system. Experiment with different knowledge bases to see how discovery is altered by the availability of new techniques.

7. Test the structure on several other areas of genetics.

B. Justification and Requirements for Continued SUMEX Use

The MOLGEN project depends heavily on the SUMEX facility. We have already developed several useful tools on the facility and are continuing research toward applying the methods of artificial intelligence to the field of molecular biology. The community of potential users is growing nearly exponentially as researchers from most of the biomedical-medical fields become interested in the technology of recombinant DNA. We believe the MOLGEN work is already important to this growing community and will continue to be important. The evidence for this is an already large list of pilot exo-MOLGEN users on SUMEX.

We support with great enthusiasm the acquisition of satellite computers for technology transfer and hope that the SUMEX staff continues to develop and support these systems. One of the oft-mentioned problems of artificial intelligence research is exactly the problem of taking prototypical systems and applying them to real problems. SUMEX gives the MOLGEN project a chance to conquer that problem and potentially supply scientific computing resources to a national audience of biomedical-medical research scientists.

II.A.1.5. ONCOCIN Project

ONCOCIN Project

Edward H. Shortliffe, M.D., Ph.D.
Departments of Medicine and Computer Science
Stanford University

I. SUMMARY OF RESEARCH PROGRAM

A. Project Rationale

The ONCOCIN Project is one of many Stanford research programs devoted to the development of knowledge-based expert systems for application to medicine and the allied sciences. The central issue in this work has been to develop a program that can provide advice similar in quality to that given by human experts, and to insure that the system is easy to use and acceptable to physicians. The work seeks to improve the interactive process, both for the developer of a knowledge-based system, and for the intended end user. In addition, we have emphasized clinical implementation of the developing tool so that we can ascertain the effectiveness of the program's interactive capabilities when it is used by physicians who are caring for patients and are uninvolved in the computer-based research activity.

B. Medical Relevance and Collaboration

The lessons learned in building prior production rule systems have allowed us to create a large oncology protocol management system much more rapidly than was the case when we started to build MYCIN. We introduced ONCOCIN for use by Stanford oncologists in May 1981. This would not have been possible without the active collaboration of Stanford oncologists who helped with the construction of the knowledge base and also kept project computer scientists aware of the psychological and logistical issues related to the operation of a busy outpatient clinic.

C. Highlights of Research Progress

C.1 Background and Overview of Accomplishments This Past Year

In the following list we have summarized the research and performance goals for the program, citing those which have been completely or partially accomplished and indicating those that have yet to be achieved:

1. to assist with identification of current protocols that may apply to a given patient [not yet undertaken; will not be relevant until more protocols than lymphomas have been encoded for routine use]

2. to assist with determining a patient's eligibility for a given protocol [not yet undertaken];

3. to provide detailed information on protocols in response to questions from clinic personnel [a query system has been developed and described in the medical computing literature; this initial system is designed for those building a protocol knowledge base; later versions will be used by physicians themselves];

4. to assist with chemotherapy dose selection and attenuation for a given patient [fully implemented and evaluated for patients under treatment for lymphoma; breast cancer protocols were recently implemented and released for use in the clinic; protocols for oat cell carcinoma complete, but not yet tested for release];

5. to provide reminders, at appropriate intervals, of follow-up tests and films required by the protocol in which a given patient is enrolled [fully implemented and evaluated for patients under treatment using ONCOCIN];

6. to reason about managing current patients in light of stored data from previous visits of (a) the individual patients [partially achieved, but much work remains; new funding has recently allowed us to undertake this task], or (b) the aggregate of all "similar" patients [not yet attempted].

7. to transfer the prototype system from its current research computer to a professional workstation that provides a model for cost-effective dissemination of clinical consultation systems [this is presently one of our major efforts];

8. to encode and implement for use by ONCOCIN the commonly used chemotherapy protocols from our oncology clinic [to facilitate this effort, a protocol acquisition system called OPAL is currently under development];

9. to develop a program to represent the therapy planning processes of expert clinicians in order to suggest treatment for patients whose special clinical situation precludes following the standard protocol [this effort was recently funded, and research has just commenced].

During the first year of this research (1979-1980), we developed a prototype of the ONCOCIN consultation system, drawing from programs and capabilities developed for the EMYCIN system-building project. During that year, we also undertook a detailed analysis of the day-to-day activities of the Stanford Oncology Clinic in order to determine how to introduce ONCOCIN with minimal disruption of an operation which is already running smoothly. We also spent much of our time in the first year giving careful consideration to the most appropriate mode of interaction with physicians in order to optimize the chances for ONCOCIN to become a useful and accepted tool in this specialized clinical environment.

The following year we completed the development of a special interface program that responds to commands from a customized keypad. We also encoded the rules for one more chemotherapy protocol (oat cell carcinoma of the lung) and updated the Hodgkin's Disease protocols when new versions were released late in 1980; these exercises demonstrated the generality and flexibility of the representation scheme we had devised. Software protocols were developed for achieving communication between the interface program and the reasoning program, and we coordinated the printing routines needed to produce hard copy flow sheets, patient summaries, and encounter sheets. Finally, lines were installed in the Stanford Oncology Day Care Center, and, beginning in May 1981, eight fellows in oncology began using the system three mornings per week for management of their patients enrolled in lymphoma chemotherapy protocols.

During our third year (1981 - 1982) the results of our early experience with physician users guided both our basic and applied work. We designed and began to collect data for three formal studies to evaluate the impact of ONCOCIN in the clinic. This latter task required special software development to generate special flow sheets and to maintain the records needed for the data analysis. Towards the end of 1982 we also began new research into a ***critiquing model*** for ONCOCIN that involves "hypothesis

assessment" rather than formal advice giving. Finally, in 1982 we began to develop a query system to allow system builders as well as end users to examine the growing complex knowledge base of the program.

Our fourth year (1982-1983) saw the departure of Carli Scott, a key figure in the initial design and implementation of ONCOCIN, the promotion of Miriam Bischoff to Chief Programmer, and the arrival of Christopher Lane as our second scientific programmer. At this time we began exploring the possibility of running ONCOCIN on a single-user professional workstation and experimented with different options for data-entry using a "mouse" pointing device. Christopher Lane has become our expert on the Xerox workstations that we are using, and most of the systems work and conversion effort described in Section C.2 below was designed or implemented by him. In addition, since ONCOCIN had grown to such a large program with many different facets, we spent much of our fourth year documenting the system. During that year we also modified the clinic system based upon feedback from the physician-users, made some modifications to the rules for Hodgkin's disease based upon changes to the protocols, and completed several evaluation studies.

ONCOCIN continues to be used routinely in the Stanford Oncology Clinic. Although it was originally made available only on three mornings per week, we have expanded the available time so that ONCOCIN may be used any time that the SUMEX 2020 computer on which it runs is not reserved for use by other research groups. The continued dependence on this time-shared computer, however, has prevented us from using ONCOCIN in in many clinical problem areas (other than the lymphomas where clinics are held three mornings per week, and breast cancer where clinic is held one day per week) because of our inability to assure the system's availability with reasonable response time at times other than the three mornings per week that SUMEX allows us to reserve the 2020. It is this latter point that has accounted for our decision not to spend a great deal of time developing new protocols to run on the 2020. Instead we have pressed our effort to adapt ONCOCIN to run on professional workstations (specifically the Xerox 1108 "Dandelion") which can eventually be dedicated to full time clinic use. We envision these workstations as the model for eventual dissemination of this kind of technology, and have been granted additional funding from DRR for three years to support workstation development along with knowledge base development so that we can add all of the protocols in use at the Stanford oncology clinic to ONCOCIN.

During the project's fifth year, three new full-time staff members, three students, and a new oncologist (Dr. Joel Bernstein) have joined our group. We are pleased that Dr. Robert Carlson, who was our Clinical Specialist for the past two years, has continued his affiliation with both Stanford and our research group. In August of 1983, Larry Fagan returned to Stanford after completing his M.D. degree. He has taken over the duties of the ONCOCIN Project Director along with becoming the Co-Director of the newly formed Medical Information Sciences Program. Dr. Fagan is in charge of coordinating the day-to-day efforts of our research. An additional programmer, Jay Ferguson, joined our group in the fall to assist with the effort required to transfer ONCOCIN from SUMEX to the 1108 workstation. A fourth programmer, Joan Differding, has joined our staff to work on our protocol acquisition effort. Samson Tu, a graduate student in Computer Science, John Williams, a medical student, and Mark Nakamura an undergraduate, are now working on ONCOCIN as well.

Funding from the NLM will continue to support the more basic research activities regarding biomedical knowledge representation, knowledge acquisition, therapy planning, and explanation as it relates to the ONCOCIN task domain. A grant from the NLM to study the therapy planning process was received, and this work (led by Dr. Fagan) has

commenced. This research is investigating how to represent the therapy planning strategies used to decide treatment for patients on the oat cell carcinoma protocol who run into serious problems requiring consultation with the protocol study chairman. Dr. Branimar Sikic, a faculty member from the Stanford University Department of Medicine, and the Study Chairman for the oat cell protocol, is collaborating on this project. A prototype system is being developed by John Williams.

In the following sections we will list our research goals and summarize recent research and development activities in greater detail.

C.2 Goal: To transfer the oncology prototype from the SUMEX research computer to a professional workstation

We have concentrated on five steps in the process of transferring the program to a professional workstation, each of which is discussed below. The transfer is from the SUMEX mainframe DEC-2020 running the INTERLISP-10 computer language to the XEROX 1108 scientific processor (called a "D-machine") running the INTERLISP-D programming language.

C.2.1 Development of a new physician interface for the graphics-oriented workstation

A major key to ONCOCIN's acceptance is the ability of the program to interface in a convenient fashion with the physician users. To reach this end we have designed a special computer graphics interface, called the Interviewer, that combines an exact replica of the familiar paper record with an advanced use of electronic pointing devices and electronic feedback.

During the last year we made major improvements to the D-Machine Interviewer program. The ONCOCIN Interviewer now has the ability to display historical information, to move back to older information not currently displayed on the computer screen, and an improved ability to select choices through multi-layered menus. Internally, it has been improved with a region based window system which increases both speed and flexibility. The region based window system, the register input devices, and the formatting language interface (that describes how forms should be presented on the display) have been generalized to be usable by other portions of the ONCOCIN project (notably the OPAL knowledge acquisition interface described below).

C.2.2 Development of new program to connect the physician interface to the reasoning portion of the program

The ONCOCIN system uses a special design that allows the Interviewer program and the reasoning section of the program to operate independently. In order to coordinate the activities of these two programs, a special communication program, called the Interactor was designed and built.

The Interactor program provides a message passing facility between two or more Interlisp-D processes (sub-programs that can run at the same time). The form of the messages are specified by the programmer. The system further allows messages to processes running on different machines via the computer network called the ETHERNET. This will allow moving components of a large program from one to several machines in a way invisible to the programs themselves. The Interactor also has the ability to find other Interactors on the local communication network.

C.2.3 Development of new programs to improve the efficiency and capabilities of ONCOCIN

In order to speed up both versions of the ONCOCIN system, we have written a simple rule and control block compiler for ONCOCIN that converts rules and control blocks into Interlisp programs, and then into compiled Interlisp. This helps to alleviate a memory space problem we have had in the Interlisp-10 version of the system as well as give us increased speed in the workstation version of the program.

Another systems level aspect of our work is in the creation and access of efficient patient record data files. To this end, we have implemented a machine independent hash file system (special data record format) that allows access to the data base via memory from disk files. The system is compatible with both Interlisp-10 and Interlisp-D and allows sharing of files between the two systems. Its format is also machine independent enough to allow access from other lisps on other computers. It is currently accepted by XEROX as a standard for the D machines and has been used by them to bring up programs of use by all D machine users. Along the same lines, we have experimented with solutions to the problems of having portions of text easily accessible by key from a file in a machine independent way.

C.2.4 Reorganization and recoding of existing programs for improved efficiency

The reasoning portion of the ONCOCIN program is being reprogrammed to increase speed and to benefit from the special capabilities of the Interlisp workstation. We are also re-writing parts of the program that were borrowed from other expert systems developed by our group.

We have reorganized the system into logical subsystems that are of a manageable size. This consisted of categorizing all the system functions (portions of the program) that are necessary for the Reasoner to run and putting each in an appropriate file. The Reasoner now runs in stand alone mode independently of which system it is on.

We are now in the process of cleaning up the specific programming part for each of the subsystems. This entails making various enhancements for both style and efficiency, adding comments and documentation, and further breaking down functionally independent parts of the system.

We have transferred portions of our EMYCIN utilities (based on the MYCIN expert system) and rewritten those utilities to make them work in both Interlisps. We have removed from the stand-alone Reasoner sections of the program that depended on the specific hardware of the DEC-2060 mainframe computer and now have versions of ONCOCIN on the 2060 and D-machines that are identical, being generated from the same program text. This step also included the use of the new hash file system (described above) on the D-machines.

C.2.5 System support for the reorganization

We have implemented a program called ***Graphcalls*** which allows programmers on the D-machines to visually graph the structure of the programs they have written. One can also examine the use of each of the functions on the graph as well as examine and change the variables they access. It also provides visual tracing and dynamic control of a program in execution. It has been used daily since its creation by both our project and members of the SUMEX community.

C.3 Goal: To modify the 2020 Clinic Version of ONCOCIN in response to user feedback

During the last year, we have added a number of new options to ONCOCIN for use by the fellows in the clinic. These include: a special option to request that a test be

ordered STAT (immediately), special menus for entering reasons for treatment modifications (these are used when there is a disagreement between the ONCOCIN recommended therapy and the physician's treatment plan, in order to gather data about why the physician has decided to override the system), and the option to request a copy of a patient's flowsheet be printed out on the clinic line-printer. We have also streamlined the methods that the various forms are created by ONCOCIN.

C.4 Goal: To encode and implement for use by ONCOCIN the commonly used chemotherapy protocols from our oncology clinic

We have pursued two approaches to increasing the number of protocols known by our system. The first approach is to use the existing software to implement active protocols not encoded at the time of our last report. The second approach has been to develop new software that is able to dramatically speed up the entry of protocols by providing graphically-oriented forms to be filled out on the computer that follow the basic outline of the protocol documents.

In the past, adding a new protocol to the ONCOCIN knowledge base has been a tedious process in which an oncologist and a programmer sit down and translate the oncologist's knowledge about the protocol into rules accessible to ONCOCIN. All the rules pertaining to the new protocol are written at that time, and this process must be repeated for every new protocol that is added to ONCOCIN. This method is rather inefficient since many of the rules are similar between protocols, differing only in their data content. To speed the process of knowledge acquisition, a program is being developed whereby a doctor could sit down at a terminal and fill in a series of forms containing appropriate questions about a new protocol. The information entered would take care of the large number of general rules pertaining to the protocol and allow the doctor and programmer to concentrate on the special cases.

The program will have two levels, the first of which is the program that will interact directly with the doctor. This program runs on Xerox D machines which have extensive graphics capabilities. Sections of the display screen (called windows) are organized in a way that emulates the physician's patterns of thought when thinking about the protocol. Other graphical entry devises have been used to encourage pointing at the answer rather than text entry. These methods are able to display all of the possible choices in a compact and comprehensible way. The first phase of this program has been completed and has been examined and approved by our oncology collaborators.

Information entered in the top level program will be converted to an intermediate data structure which will be used by the second level of the program to make new rules for the ONCOCIN knowledge base. Eventually, this process will also work in the opposite direction so that information about a previously entered protocol can be copied or modified by the physician for the new protocol. This "similar to" option will also extend to chemotherapies and drugs, so that when the doctor enters a chemotherapy or drug that the system knows about, pertinent information will be filled in for the doctor to copy or modify. The "similar to" capably along with the use of graphical input devices to speed the process of entering a new protocol and will also reduce errors and duplications. When this project is completed the total time needed to enter a new protocol should be greatly reduced and more effort will be concentrated on fine tuning the rules to handle special situations.

C.5 Evaluations of ONCOCIN's Performance

Data collection and analysis for all three ONCOCIN evaluations are now complete, results were presented at the annual meeting of the Society for Medical Decision Making, and we expect to have formal reports published during the next year.

Study 1, overseen by Dr. Robert Carlson of the Division of Oncology, is an evaluation of the program's impact on the attitude of the oncology fellows towards computers in general and ONCOCIN in particular. All physicians were administered questionnaires and structured interviews in the Spring of 1981 before ONCOCIN was introduced. The same questionnaires were distributed to them again after they had used the system for over a year. Follow-up interviews were also undertaken. This study was repeated again during 1983 to determine the trends over time. The results of this study are presently being prepared as a formal report.

We are also revising this study in preparation for the integration of the workstation version of ONCOCIN into the clinic. To maintain some consistency in the evaluation process, the original questions from Study 1 will be given and analyzed as before along with new questions. Several of these new survey and interview questions will serve as a "baseline" for evaluating any perceived improvements that will come with the introduction of the professional workstations in the clinic.

Study 2, overseen by Dr. Daniel Kent of the Division of General Internal Medicine, is an evaluation of the program's impact on the completeness and accuracy of flowsheet data recorded with and without ONCOCIN. Research programmers wrote routines to formally analyze on-line flow sheets for completeness and accuracy. Pre-ONCOCIN flow sheets were then entered into the system ***exactly as they were originally recorded by the physician***. The same analytic routines were used to analyze these pre-ONCOCIN flow sheets. The pre- and post- ONCOCIN data were compared. Results indicate that ONCOCIN has had a statistically significant beneficial impact on the completeness of data recording, the ordering of required tests, and the accuracy of the data recorded. A formal report of the results is in preparation.

Finally, Study 3 is examining the comparison between ONCOCIN's therapeutic advice and the treatment decisions made by oncology fellows in the same setting. The study was coordinated by Dr. David Hickam, formerly of our Division of General Internal Medicine and now on the faculty at the University of Oregon in Portland. Expert evaluators rated treatment plans without knowing whether the recommendation was that of ONCOCIN or one of the clinic physicians. Over 200 flow sheets were evaluated by Stanford lymphoma experts, and the resulting data have been fully analyzed by Dr. Hickam. The results indicate that the experts were unable to fault the recommendations made by ONCOCIN relative to those of experienced oncology fellows treating patients with lymphoma. A paper describing the results is in preparation.

A study was made of all of the cases run by physicians in the clinic to determine statistics about when they chose to override ONCOCIN's therapy recommendation. The results showed that approximately 75% of the time they agreed completely. When there were disagreements, 15% were about individual drug doses. This study pointed out a number of situations where ONCOCIN needs more knowledge, and where our expert needed clarification from the Principal Investigators of the particular protocol. As a result, a meeting was held (7/12/83) with some of the Faculty in charge of the Hodgkin's protocols to discuss issues arising from this study.

C.6 Documentation

An extensive effort to document the ONCOCIN system was completed during this last year. Many aspects of the ONCOCIN program and its programming environment are now written and available for project members' use. The increase in documentation has significantly reduced the start-up time for new researchers working with the project. In addition, we have published several papers and prepared several technical reports describing the system.

C.7 Hypothesis Assessment

As mentioned above, largely through the efforts of Curtis Langlotz, we have continued to develop modifications to ONCOCIN that will permit it to function as an "observer" of the physician's own decisions rather than as a primary source of advice. By permitting the physician to enter his or her own therapy plan on the flowsheet, we can acknowledge the oncologist's ability to reach appropriate therapeutic decisions for most patients. ONCOCIN will simply compare the physician's plan with what it believes is the proper therapy. If the system agrees with the physician, or determines that small differences are clinically insignificant, no advice from the computer will be necessary. If significant disagreements occur, on the other hand, ONCOCIN will need to respond with warnings and explanations for why it feels that an alternate therapy plan may be preferable. Our experience with ONCOCIN since its clinic implementation suggests that this mode of interaction will be preferred by the clinic physicians. It will require minimal changes to ONCOCIN's decision making approach, but the determination of what differences are clinically significant, and the optimal method for explaining their importance to the physician, are exciting challenges and important theoretical problems. An initial report describing this work appeared during 1983 in the ***International Journal of Man-Machine Studies***, and we plan to continue enhancing the system's critiquing and explanation capabilities. Mr. Langlotz presented this work in the 1983 Society for Computer Applications in Medical Care Conference Student Paper Competition, and was a finalist in the competition. The approach will not be used in the clinic, however, until ONCOCIN has been transferred to professional workstations, hopefully in about two years.

C.7 Query System and Rule Analysis

Shoko Tsuji has completed her work on the development of a query system to permit easy access to the large ONCOCIN knowledge base. Once we had encoded several hundred rules, it became unwieldy for system builders to work from large hard-copy listings of the knowledge base, and we anticipate that physicians will also require direct access to the program's knowledge. The query system permits this kind of access. Rather than dealing with natural language understanding by computer, we are designing ways that menu selection and the high-speed interface can be used to permit access to the information that is needed by a physician or system builder. A paper describing the early work was presented last year (May 1983) at the *AAMSI Congress 83* in San Francisco.

In previous reports we also described the work of Dr. Motoi Suwa who developed programs to assist in determining knowledge base consistency and completeness. His paper on this subject appeared in late 1982 in the *AI Magazine*. However, the programs that he wrote were never formally linked to our system for writing rules and modifying other parts of the knowledge base. As a result, Mr. Robert Noble spent time during the last few years modifying Suwa's code so that it would operate as an integral part of ONCOCIN. These changes have now been implemented so that a new rule can be dynamically compared to the rest of the knowledge base during the process of knowledge entry. Mr. Noble is currently considering how such a program might be implemented on a workstation in order to take advantage of the newly available graphical capabilities of these machines.

C.9 Encoding of Additional Protocols

As was indicated above, we have emphasized transfer of ONCOCIN to a professional workstation rather than the implementation of additional protocols. However, the oncologist in charge of breast cancer treatment at Stanford had expressed great interest in adding those treatment protocols to the system as soon as possible. We

have accordingly encoded and thoroughly tested the treatment plans for adjuvant therapy of breast carcinoma (CMF and CMFVP treatment plans) and released them for regular use in the spring of this year. Encoding of the CMF treatment plan required encoding of special rule types. In order to represent these treatment plans special methods were created for looking back to previous cycles to compare current laboratory results to previous values. This allows the development of treatment recommendations based upon past experience with the patient. A number of other protocols were added to the ONCOCIN system in order to keep the system's knowledge about Hodgkin's and Lymphoma protocols current. These included new Lymphoma protocols with very complex alternating chemotherapies (M-HOP/B-Cepp/HD-MTX and M-BACOD/HD-MTX), and new Hodgkin's protocols (alternating MOPP/ABVD).

C.10 Strategic Therapy Planning

As mentioned above, we have begun a new research project to study the therapy planning process, and how strategies which are used to plan therapy in difficult cases might be represented on a computer. This project, which we call the ONYX project, has as its goals: to conduct basic research into the possible representations of the therapy planning process; to develop a computer program to represent this process; and eventually to interface the planning program with ONCOCIN. The project members (Fagan, Bischoff, Williams, Langlotz, and Rennels) have spent many hours meeting with Dr. Sikic trying to understand how he plans therapy for patients whose special clinical situation precludes following the standard therapeutic plan described in the protocol document. In March of this year, the group spent two days at Xerox Palo Alto Research Center (PARC), working with Mark Stefik, Daniel Bobrow and Sanjay Mittal of PARC on possible representations for the knowledge structures and how such a program might run using the LOOPS knowledge programming system. We hope to have a prototype of this system running this year.

D. Publications Since January 1983

1. (*) Shortliffe, E.H. and Fagan, L.M. Expert systems research: modeling the medical decision making process. In: ***An Integrated Approach to Monitoring*** (J.S. Gravenstein, R.S. Newbower, A.K. Ream, and N.T. Smith, eds.), pp. 183-200, Woburn, MA: Butterworth's, 1983.

2. Duda, R.O. and Shortliffe, E.H. Expert systems research. ***Science,*** 220:261-268 (1983).

3. (*) Langlotz, C.P. and Shortliffe, E.H. Adapting a consultation system to critique user plans. ***International Journal of Man-Machine Studies,*** 19:479-496 (1983).

4. (*) Tsuji, S. and Shortliffe, E.H. Graphical access to the knowledge base of a medical consultation system. ***Proceedings of AAMSI Congress 83,*** pp 551-555, San Francisco, CA, May 1983.

5. (*) Bischoff, M.B., Shortliffe, E.H., Scott, A.C., Carlson, R.W. and Jacobs, C.D. Integration of a computer-based consultant into the clinical setting. ***Proceedings 7th Annual Symposium on Computer Applications in Medical Care***, pp. 149-152. October 1983, Baltimore, Maryland.

6. Mulsant, B. and Servan-Schreiber, D.: Knowledge engineering: a daily activity on a hospital ward. ***Computers and Biomedical Research*** 17:71-91 (1984).

7. (*) Shortliffe, E.H. Problems in implementing the computer for continuing education. Mobius. 3:52-55 (1983).

8. Shortliffe, E.H. The science of biomedical computing. In *Meeting the Challenge: Informatics and Medical Education* (J.C. Pages, A.H. Levy, F. Gremy, and J. Anderson, eds.), pp 1-10, Amsterdam, North-Holland, 1983.

9. Six Abstracts: Studies to Evaluate the ONCOCIN System.

- Shortliffe, E.H., Bischoff, M.B., Carlson, R.W., Jacobs, C.D. Clinical Integration to promote use and acceptance of a computer-based consultant. Presented at Annual Meeting Society for Medical Decision Making, Toronto, Canada, October 1983; reprinted in *Medical Decision Making* 3:358 (1983).

- Hickam, D.H., Shortliffe, E.H., Jacobs, C.D. A blinded evaluation of computer-based cancer chemotherapy treatment advice. *Clinical Research* 31(2):297A (1983).

- Hickam, D.H., Shortliffe, E.H. and Jacobs, C.D. An evaluation of the treatment recommendations of a computer-based cancer chemotherapy protocol advisor. Presented at Annual Meeting Society for Medical Decision Making, Toronto, 1983; reprinted in *Medical Decision Making* 3:362 (1983).

- Kent, D.L., Shortliffe, E.H., Bischoff, M.B. and Jacobs, C.D. The impact on quality of data management of a computer-based consultant program. Presented at Annual Meeting Society for Medical Decision Making, Toronto, October 1983; Reprinted in *Medical Decision Making* 3:362 (1983).

- Kent, D.L., Carlson, R.W., Jacobs, C.D. and Shortliffe, E.H. Evaluation of computer-based interactive data management for clinical trails. Presented at Annual meeting of the Western Section American Federation for Clinical Research, Carmel, February 1984; Reprinted in *Clinical Research* 32:31A (1984).

- Carlson, R.W., Shortliffe, E.H., Jacobs, C.D., Koretz, M.M. Physician attitudes toward a computer-based expert oncology consulting system. Submitted to Annual Meeting American Society for Clinical Oncology, Toronto, May 1984.

E. Funding Support

Grant Title: "Research Program: Biomedical Knowledge Representation"
Principal Investigator: Edward A. Feigenbaum
Co-Principal Investigator (ONCOCIN Project): Edward H. Shortliffe
Agency: National Library of Medicine
ID Number: LM-03395
Term: July 1979 to June 1984
Total award: $497,420
Current award (1983-1984): $95,424

Grant Title: "Symbolic Computation Methods For Clinical Reasoning" (RCDA)
Principal Investigator: Edward H. Shortliffe
Agency: National Library of Medicine
ID Number: LM-00048
Term: July 1979 to June 1984

Total award: $196,425
Current award (1983-1984): $39,502

Grant Title: "The Development of Representation Methods to Facilitate Knowledge Acquisition and Exposition in Expert Systems"
Principal Investigator: Edward H. Shortliffe
Agency: Office of Naval Research
ID Number: NR 049-479
Term: January 1981 to December 1983
Total award: $456,622 (includes indirect costs)

Grant Title: "Studies in the Dissemination of Consultation Systems"
Principal Investigator: Edward H. Shortliffe
Agency: Biotechnology Resources Program, Division of Research Resources
ID Number: RR 01613
Term: July 1983 to June 1986
Total award: $624,455
Current award: (7/83-6/84): $220,371

Grant Title: "Therapy-planning strategies for consultation by computer"
Principal Investigator: Edward H. Shortliffe
Agency: National Library of Medicine
ID Number: LM-04136
Term: August 1983 to July 1986
Total award: $211,851
Current award: (8/83-7/84) $60,517

Grant Title: Henry J. Kaiser Faculty Scholar in General Internal Medicine
Principal Investigator: Edward H. Shortliffe
Agency: Henry J. Kaiser Family Foundation
Term: July 1983 to June 1986, renewable until June 1988
Total award: $150,000 ($50,000 annually).

Grant Title: Research on Introspective Systems
Principal Investigator: Michael R. Genesereth
Co-Principal Investigator: Edward H. Shortliffe
Agency: Office of Naval Research
ID Number: N00014-81-K-0004
Term: January 1, 1984 - December 31, 1986
Total award: $512,070 (includes indirects)

Grant Title: Information structure and use in knowledge-based expert systems
Principal Investigator: Bruce G. Buchanan
Co-Principal Investigator: Edward H. Shortliffe
Agency: National Science Foundation - IST83-12148
Term: March 1, 1984 - February 28, 1987
Total award: $330,000 (includes indirects)

II. INTERACTIONS WITH THE SUMEX-AIM RESOURCE

A. Medical Collaborations and Program Dissemination via SUMEX

A great deal of interest in ONCOCIN has been shown by the medical, computer science, and lay communities. We are frequently asked to demonstrate the program to Stanford visitors (both the prototype system running in the clinic and the newer work transferring the system to professional workstations). We also demonstrated some of the developing workstation code on a machine loaned by the Xerox Corporation and installed at the *AAMSI Congress 83* held in San Francisco in May 1983. Physicians have generally been enthusiastic about ONCOCIN's potential. The interest of the lay community is reflected in the frequent requests for magazine interviews and television coverage of the work. Articles about MYCIN and ONCOCIN have appeared in such diverse publications as *Time* and *Fortune*, whereas ONCOCIN has been featured on the "NBC Nightly News", the PBS "Health Notes" series, and "The MacNeil-Lehrer Report." Due to the frequent requests for ONCOCIN demonstrations, we are producing a videotape about the ONCOCIN research which will include demonstrations of our the professional workstation research projects and the 2020-based clinic system. We have completed filming of the workstation demonstration programs and are ready to start filming the current clinic system and other necessary sequences. We expect the videotape to be complete by the summer and plan to make it available to interested SUMEX collaborators and other interested persons.

Our group also continues to oversee the MYCIN program (not an active research project since 1978) and the EMYCIN program. Both systems continue to be in demand as demonstrations of expert systems technology. MYCIN been demonstrated via networks at both national and international meetings within the last year, and several medical school and computer science teachers continue to use the program in their computer science or medical computing courses. We also have made the MYCIN program available to researchers around the world who access SUMEX using the GUEST account. EMYCIN has been made available to interested researchers developing expert systems who access SUMEX via the CONSULT account. One such consultation system for psychopharmacological treatment of depression, called Blue-Box, developed by two French medical students, Benoit Mulsant and David Servan-Schreiber, was reported on in July of 1983 in *Computers and Biomedical Research.*

B. Sharing and Interaction with Other SUMEX-AIM Projects

The community created on the SUMEX resource has other benefits that go beyond actual shared computing. Because we are able to experiment with other developing systems, such as INTERNIST/CADUCEUS, and because we frequently interact with other workers (at AIM Workshops or at other meetings), many of us have found the scientific exchange and stimulation to be heightened. Several of us have visited workers at other sites, sometimes for extended periods, in order to pursue further issues which have arisen through SUMEX- or Workshop-based interactions. In this regard, the ability to exchange messages with other workers, both on SUMEX and at other sites, has been crucial to rapid and efficient exchange of ideas. Certainly it is unusual for a small community of researchers with similar scholarly interests to have at their disposal such powerful and efficient communication mechanisms, even among those on opposite coasts of the country.

C. Critique of Resource Management

The transition from Tom Rindfleisch's able leadership to the directorship of Ed Pattermann went extremely smoothly, especially when one considers the simultaneous changeover to a new mainframe machine in early 1983. Our community of researchers has been extremely fortunate to work on a facility that has continued to maintain the high standards that we have praised in the past. The staff members are always helpful

and friendly, and work as hard to please the SUMEX community as to please themselves. As a result, the computer is as accessible and easy to use as they can make it. More importantly, it is a reliable and convenient research tool. We extend special thanks to Ed Pattermann for maintaining such high professional standards.

III. RESEARCH PLANS

A. Project Goals and Plans

In the coming year, there are seven areas in which we expect to expend our efforts on the ONCOCIN System:

1. We will complete preparation of, and submit for publication, papers describing the three ONCOCIN evaluations.
2. We will complete the filming and editing of a videotape about the ONCOCIN research.
3. We will continue to spend time maintaining the system's documentation and will prepare additional formal technical reports as well as the clinical reports on the evaluation studies.
4. We will continue to develop the hypothesis assessment approach to consultation (the ***critiquing model***) that was described above.
5. We will continue our efforts to transfer ONCOCIN to professional workstations and will begin planning for their implementation in the oncology clinic.
6. We will continue our efforts to develop a protocol acquisition system and begin to enter the other treatment protocols in use in the oncology clinic.
7. We will continue our basic research into the therapy planning process and develop a prototype system to assist with therapy planning.

B. Justification and Requirements for Continued SUMEX Use

All the work we are doing (ONCOCIN plus continued use of the original MYCIN program) is totally dependent on continued use of the SUMEX resource. Although some of the ONCOCIN work is shifting to Xerox workstations, the SUMEX 2060 and the 2020 continue to be key elements in our research plan. The programs all make assumptions regarding the computing environment in which they operate, and the ONCOCIN prototype in particular depends upon proximity to the DEC 2020 which enables us to use a 9600 baud interface.

In addition, we have long appreciated the benefits of GUEST and network access to the programs we are developing. SUMEX greatly enhances our ability to obtain feedback from interested physicians and computer scientists around the country. Network access has also permitted high quality formal demonstrations of our work both from around the United States and from sites abroad (e.g., Finland, Japan, Sweden, Switzerland).

We plan to continue development of ONCOCIN on both our own (recently purchased) Dandelion workstation and the shared SUMEX Dandelion workstation, and will be obtaining an additional workstation in the near future. However, the project now includes three graduate students (Langlotz, Tu, and Williams), two undergraduates (Noble, Nakamura), four full-time programmers (Bischoff, Differding, Ferguson, and Lane), a project director (Larry Fagan); in addition, new students will join us this summer and fall. Many of the students, and all of the programmers, need access to a workstation for major portions of their work. Due to the limited access to workstations, it will be necessary to continue use of the SUMEX 2060 for much of our work.

C. Requirements for Additional Computing Resources

The acquisition of the DEC 2020 by SUMEX was crucial to the growth of our research work. It has insured high quality demonstrations and has enabled us to develop a system (ONCOCIN) for real-world use in a clinical setting. As we have begun to develop systems that are potentially useful as stand-alone packages (i.e., an exportable ONCOCIN), the addition of personal workstations has provided particularly valuable new resources. We have made a commitment to the smaller Interlisp-D machines (Dandelions) produced by Xerox, and our work will increasingly transfer to them over the next several years. Our new funding will support our effort to implement ONCOCIN on workstations in the Stanford oncology clinic (and eventually to move the program to non-Stanford environments), but we will simultaneously continue to require access to Interlisp workstations made available by SUMEX for our research and development work. We are hopeful that it will be possible for SUMEX to commit to ONCOCIN considerable time on the new SUMEX workstations being acquired at the end of the current grant year.

The acquisition of the DEC 2060, coupled with our increasing use of workstations, has greatly helped with the problems in SUMEX response time that we had described in previous annual reports. We are extremely grateful for access both to the new central machine and to the research workstations on which we are currently building the new ONCOCIN prototype. The D-machine's address space is permitting development of the large knowledge base that ONCOCIN requires. The graphics capability of the workstations has also enabled us to develop new methods for presenting material to naive users. In addition, the D-machines have provided a reliable, constant "load-average" machine for running experiments with physicians and doing development work. The development of ONCOCIN on the Dandelion will demonstrate the feasibility of running intelligent consultation systems on small, affordable machines in physicians' offices and other remote sites.

D. Recommendations for Future Community and Resource Development

SUMEX is providing an excellent research environment and we are delighted with the help that SUMEX staff have provided implementing enhanced system features on the 2060 and on the workstations. We feel that we have a highly acceptable research environment in which to undertake our work. Workstation availability is becoming increasingly crucial to our research, and we have found over the past year that workstation access is at a premium. The SUMEX staff has been very helpful and understanding about our needs for workstation access, allowing us Dandelion use wherever possible, and providing us with systems-level support when needed. We look forward to the arrival of additional workstations and the development of a more distributed computing environment through SUMEX-AIM.

II.A.1.6. RADIX Project

The RADIX Project: Deriving Medical Knowledge from Time-Oriented Clinical Databases

Robert L. Blum, M.D., Ph.D.
Department of Computer Science
Stanford University

Gio C. M. Wiederhold, Ph.D.
Departments of Computer Science and Medicine
Stanford University

I. SUMMARY OF RESEARCH PROGRAM

A. Technical Goals - Introduction

Medical and Computer Science Goals -- The long range objectives of our project, called RADIX (formerly RX), are 1) to increase the validity of medical knowledge derived from large time-oriented databases containing routine, non-randomized clinical data, 2) to provide knowledgeable assistance to a research investigator in studying medical hypotheses on large databases, 3) to fully automate the process of hypothesis generation and exploratory confirmation. For system development we have used a subset of the ARAMIS database.

Computerized clinical databases and automated medical records systems have been under development throughout the world for at least a decade. Among the earliest of these endeavors was the ARAMIS Project, (American Rheumatism Association Medical Information System) under development since 1969 in the Stanford Department of Medicine. ARAMIS contains records of over 17,000 patients with a variety of rheumatologic diagnoses. Over 62,000 patient visits have been recorded, accounting for 50,000 patient-years of observation. The ARAMIS Project has now been generalized to include databases for many chronic diseases other than arthritis.

The fundamental objective of the ARAMIS Project as well as of all other clinical database researchers is to use the data that have been gathered by clinical observation in order to study the evolution and medical management of chronic diseases. Unfortunately, the process of reliably deriving knowledge has proven to be exceedingly difficult. Numerous problems arise stemming from the complexity of disease, therapy, and outcome definitions, from the complexity of causal relationships, from errors introduced by bias, and from frequently missing and outlying data. A major objective of the RADIX Project is to explore the utility of symbolic computational methods and knowledge-based techniques at solving some of these problems.

The RADIX computer program is designed to examine a time-oriented clinical database such as ARAMIS and to produce a set of (possibly) causal relationships. The algorithm exploits three properties of causal relationships: time precedence, correlation, and nonspuriousness. First, a Discovery Module uses lagged, nonparametric correlations to generate an ordered list of tentative relationships. Second, a Study Module uses a knowledge base (KB) of medicine and statistics to try to establish nonspuriousness by controlling for known confounders.

The principal innovations of RADIX are the Study Module and the KB. The Study Module takes a causal hypothesis obtained from the Discovery Module and produces a comprehensive study design, using knowledge from the KB. The study design is then executed by an on-line statistical package, and the results are automatically incorporated into the KB. Each new causal relationship is incorporated as a machine-readable record specifying its intensity, distribution across patients, functional form, clinical setting, validity, and evidence. In determining the confounders of a new hypothesis the Study Module uses previously "learned" causal relationships.

In creating a study design the Study Module follows accepted principles of epidemiological research. It determines study feasibility and study design: cross-sectional versus longitudinal. It uses the KB to determine the confounders of a given hypothesis, and it selects methods for controlling their influence: elimination of patient records, elimination of confounding time intervals, or statistical control. The Study Module then determines an appropriate statistical method, using knowledge stored as production rules. Most studies have used a longitudinal design involving a multiple regression model applied to individual patient records. Results across patients are combined using weights based on the precision of the estimated regression coefficient for each patient.

B. Medical Relevance and Collaboration

As a test bed for system development our focus of attention has been on the records of patients with systemic lupus erythematosus (SLE) contained in the Stanford portion of the ARAMIS Data Bank. SLE is a chronic rheumatologic disease with a broad spectrum of manifestations. Occasionally the disease can cause profound renal failure and lead to an early death. With many perplexing diagnostic and therapeutic dilemmas, it is a disease of considerable medical interest.

In the future we anticipate possible collaborations with other project users of the TOD System such as the National Stroke Data Bank, the Northern California Oncology Group, and the Stanford Divisions of Oncology and of Radiation Therapy.

We believe that this research project is broadly applicable to the entire gamut of chronic diseases that constitute the bulk of morbidity and mortality in the United States. Consider five major diagnostic categories responsible for approximately two thirds of the two million deaths per year in the United States: myocardial infarction, stroke, cancer, hypertension, and diabetes. Therapy for each of these diagnoses is fraught with controversy concerning the balance of benefits versus costs.

1. Myocardial Infarction: Indications for and efficacy of coronary artery bypass graft vs. medical management alone. Indications for long-term antiarrhythmics ... long-term anticoagulants. Benefits of cholesterol-lowering diets, exercise, etc.

2. Stroke: Efficacy of long-term anti-platelet agents, long-term anticoagulation. Indications for revascularization.

3. Cancer: Relative efficacy of radiation therapy, chemotherapy, surgical excision - singly or in combination. Optimal frequency of screening procedures. Prophylactic therapy.

4. Hypertension: Indications for therapy. Efficacy versus adverse effects of chronic antihypertensive drugs. Role of various diagnostic tests such as renal arteriography in work-up.

5. Diabetes: Influence of insulin administration on microvascular complications. Role of oral hypoglycemics.

Despite the expenditure of billions of dollars over recent years for randomized controlled trials (RCT's) designed to answer these and other questions, answers have been slow in coming. RCT's are expensive of funds and personnel. The therapeutic questions in clinical medicine are too numerous for each to be addressed by its own series of RCT's.

On the other hand, the data regularly gathered in patient records in the course of the normal performance of health care delivery are a rich and largely underutilized resource. The ease of accessibility and manipulation of these data afforded by computerized clinical databases holds out the possibility of a major new resource for acquiring knowledge on the evolution and therapy of chronic diseases.

The goal of the research that we are pursuing on SUMEX is to increase the reliability of knowledge derived from clinical data banks with the hope of providing a new tool for augmenting knowledge of diseases and therapies as a supplement to knowledge derived from formal prospective clinical trials. Furthermore, the incorporation of knowledge from both clinical data banks and other sources into a uniform knowledge base should increase the ease of access by individual clinicians to this knowledge and thereby facilitate both the practice of medicine as well as the investigation of human disease processes.

C. Highlights of Research Progress

C.1 1 May 1983 to 1 May 1984

Our primary accomplishments in this period have been the following:

1) complete modifications to RADIX to accommodate the one hundred-fold increase in the size of our database to 1700 patients,

2) carry out the study of the effect of prednisone on serum cholesterol on the new database,

3) publish results of the 1700 patient prednisone/cholesterol study,

4) publish the description of a two-stage regression method adapted by us to this study,

5) complete System Programmer's Manuals and User's Manual in preparation for transfer to outside sites, and

6) begin transfer of RADIX to Xerox D-Machine personal work stations.

C.1.1 Modifications to RADIX for the enlarged database

Extensive modifications to RADIX were required to deal with the 100-fold increase in the size of the database. The modifications necessary to run the study module automatically on the prednisone/cholesterol study were completed this year.

C.1.2 Prednisone/chlosterol study on enlarged database

We have carried out the automated study of the effect of prednisone on serum cholesterol using the new 1700 patient database. It has strongly confirmed the effect previously observed in the 50-patient SLE database. In addition, we are examining the effect in non-SLE patients and in other patient subsets. We are also examining alternative pharmacokinetic models for the prednione effect using the newly available data.

C.1.3 Publish results of prednisone/cholesterol study

The paper reporting these results is in draft form. It will be submitted for publication shortly.

C.1.4 Publish description of 2-stage regression method

A description of the 2-stage regression method has been submitted for publication.

C.1.5 Documentation

A two-volume System Programmer's Manual and a User's Manual describing implementation, maintenance and use of the system at Stanford has been completed. In addition, a complete set of the files needed for on-line demonstrations has been created, separating them from the working versions.

C.1.6 Transer of RADIX to D-Machines

Preliminary work on implementing RADIX on D-Machines has begun. This will continue in coming years.

C.1.7 Other accomplishments

We have presented the results of our research at several conferences during the year. Additional publications for the year are noted in the section on publications.

C.2 Research in Progress

We are currently completing additional studies on subsets of the 1700 patient database. These include automated analysis of the prednisone/ cholesterol effect in non-SLE patients and subsets of SLE patients, and fitting alternative pharmacokinetic models of the prednisone/cholesterol effect. This work should be completed shortly. We will then return to the more AI-oriented aspects of RADIX, as described below in the section on Research Plans.

D. Publications

1. Blum, R.L.: *Two Stage Regression: Application to a Time-Oriented Clinical Database.* (Submitted for publication to the American Journal of Epidemiology.)

2. Blum, R.L.: *Prednisone Elevates Cholesterol: An Automated Study of Longitudinal Clinical Data.* (Manuscript in preparation.)

3. Blum, R.L., and Walker, M.G.: *Minimycin: A Miniature Rule-Based System* (Submitted for publication to M.D.Computing)

4. Blum, R.L.: *Modeling and encoding clinical causal relationships.* Proceedings of SCAMC, Baltimore, MD, October, 1983.

5. Blum, R.L.: *Representation of empirically derived causal relationships.* IJCAI, Karlsruhe, West Germany, August, 1983 .

6. Blum, R.L.: *Machine representation of clinical causal relationships.* MEDINFO 83, Amsterdam, August, 1983.

7. Blum, R.L.: *Clinical decision making aboard the Starship Enterprise.* Chairman's paper, Session on Artificial Intelligence and Clinical Decision Making, AAMSI, San Francisco, May, 1983.

8. Blum, R.L. and Wiederhold, G.: *Studying hypotheses on a time-oriented*

database: An overview of the RX project. Proc. Sixth SCAMC, IEEE, Washington D.C., October, 1982.

9. Blum, R.L.: *Induction of causal relationships from a time-oriented clinical database: An overview of the RX project.* Proc. AAAI, Pittsburgh, August, 1982.

10. Blum, R.L.: *Automated induction of causal relationships from a time-oriented clinical database: The RX project.* Proc. AMIA San Francisco, 1982.

11. Blum, R.L.: *Discovery and Representation of Causal Relationships from a Large Time-oriented Clinical Database: The RX Project.* IN D.A.B. Lindberg and P.L. Reichertz (Eds.), LECTURE NOTES IN MEDICAL INFORMATICS, Springer-Verlag, 1982.

12. Blum, R.L.: *Discovery, confirmation, and incorporation of causal relationships from a large time-oriented clinical database: The RX project.* Computers and Biomed. Res. 15(2):164-187, April, 1982.

13. Blum, R.L.: *Discovery and representation of causal relationships from a large time-oriented clinical database: The RX project* (Ph.D. thesis). Computer Science and Biostatistics, Stanford University, 1982.

14. Blum, R.L.: *Displaying clinical data from a time-oriented database.* Computers in Biol. and Med. 11(4):197-210, 1981.

15. Blum, R.L.: *Automating the study of clinical hypotheses on a time-oriented database: The RX project.* Proc. MEDINFO 80, Tokyo, October, 1980, pp. 456-460. (Also STAN-CS-79-816)

16. Blum, R.L. and Wiederhold, G.: *Inferring knowledge from clinical data banks utilizing techniques from artificial intelligence.* Proc. Second SCAMC, IEEE, Washington, D.C., November, 1978.

17. Blum, R.L.: *The RX project: A medical consultation system integrating clinical data banking and artificial intelligence methodologies,* Stanford University Ph.D. thesis proposal, August, 1978.

18. Kuhn, Ingeborg, Gio Wiederhold, Jonathan E. Rodnick, Diane M. Ramsey-Klee, Sanford Benett, and Donald D. Beck: *Automated Ambulatory Medical Record Systems in the U.S.*, to be published by Springer-Verlag, 1983, in Information Systems for Patient Care, B. Blum (ed.), Section III, Chapter 14.

19. Walker, M.G., and Blum, R.L.: *A Lisp Tutorial.* (Submitted for publication to M.D.Computing.)

20. Wiederhold, Gio: *Knowledge and Database Management*, IEEE Software Premier Issue, Jan.1984, pp.63--73.

21. Wiederhold,Gio: *Networking of Data Information*, National Cancer Institute Workshop on the Role of Computers in Cancer Clinical Trials, National Institutes of Health, June 1983, pp.113-119.

22. Wiederhold, Gio: *Database Design* (in the Computer Science Series) McGraw-Hill Book Company, New York, NY, May 1977, 678 pp. Second edition, Jan. 1983, 768 pp.